REMARKS

Following entry of this amendment, claims 1, 6-17, 19, and 24-33 will be pending in this application. Claims 1, 6, and 24 are currently amended; and new claims 30-33 are added. Support for the amendments and new claims can be found throughout the application as filed, e.g., at page 4, lines 1-11; page 9, line 28, to page 10, line 3; and page 15, lines 25-33. No new matter has been added.

Applicants note that Buck et al., 1999, Biotechniques, 27:528-536, which was first cited by the Office in this action, was not included on the Notice of References Cited, Form PTO-892. Applicants request that the Office issue a Notice of References cited listing this publication.

Interview Summary

Applicants thank Examiners Suchira Pande and Teresa E. Strzelecka for holding a telephonic interview with Janis K. Fraser and the undersigned on November 2, 2009. During the interview, the participants discussed the pending rejections of the claims for alleged obviousness.

Claim Objections

Claims 1 and 24 were objected to for deletion of the word "isolated" from the claims. The Office has provided no reason for the objection besides "convention". Solely in the interest of advancing prosecution, applicants have amended claims 1 and 24 to again recite "isolated" oligonucleotides. Applicants request withdrawal of the rejection.

35 USC § 103

Claim 1 was rejected as allegedly being unpatentable over Marsh et al., 1999, Genomics, 58:310-312 ("Marsh") in view of Buck et al., 1999, Biotechniques, 27:528-536 ("Buck"). Applicants respectfully traverse the rejection.

The Office action states (at page 4): "Regarding claim 1, Marsh et al. teach sequence of a region comprising the claimed sequence of the oligonucleotide identified by SEQ ID NO 1." Marsh does not disclose within its "four corners" the nucleic acid sequences alleged by the

Office, although Marsh does refer to GenBank Accession No. AF127519,[1] which the Office action appears to quote at pages 4-5. Although GenBank Accession No. AF127519 discloses a nucleic acid that comprises SEQ ID NO:1, it neither teaches nor suggests an oligonucleotide having a sequence consisting of SEQ ID NO:1, as required by the present claims.

The Office cites Buck as allegedly providing motivation to create an oligonucleotide having a sequence consisting of SEQ ID NO:1 based on the disclosure of Marsh. The Office action states (at page 5):

> It would have been prima facie obvious to one of ordinary skill in the art at the time [] the invention was made to have used the method of Buck et al. to design the [] oligonucleotide claimed in instant application as SEQ ID No 1 using the teaching of sequences of thymidylate [synthase] enhancer region taught by Marsh et al. as the starting point.

Applicants respectfully disagree that the combination of Marsh and Buck would have provided motivation to one of skill in the art to select an oligonucleotide consisting of SEQ ID NO:1. As an initial matter, Buck does not teach or suggest a method of oligonucleotide design. Rather, Buck discloses (i) a survey of laboratories that designed sequencing and PCR primers to determine what they believed to be optimal and acceptable primer characteristics; and (ii) an empirical study of primers provided by those laboratories and predicted to be effective for sequencing a specific DNA sequence, as compared to a control panel of 18-nucleotide primers that spanned the sequence. See Buck pages 529, middle column, to 530, middle column, and page 532. Applicants will discuss separately the relevance of each of these disclosures to claim 1.

First, the survey of laboratories would not have led one of ordinary skill to the oligonucleotide of claim 1. The results of the survey are summarized in Table 1 of Buck. The surveyed laboratories indicated that acceptable sequencing or PCR primers would range in length from 15 to 40 nucleotides with a G+C content of 30%-70%. Buck, Table 1. Although SEQ ID NO:1 is 27 nucleotides long, within the range of acceptable lengths, it also has a G+C content of 81%, well outside of the range of values deemed acceptable by the surveyed laboratories. Buck also discloses that the percent G+C was rated by the surveyed laboratories as one of the most

[1] A copy of GenBank Accession No. AF127519 was previously submitted to the Office in the Information Disclosure Statement submitted November 22, 2005. This listing was first available on July 15, 1999.

important characteristics to consider when designing primers. Buck, page 535, left column. The results of this survey are evidence of the conventional wisdom regarding the selection of sequencing or PCR primers, and the oligonucleotide of claim 1 does not conform to this conventional wisdom. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. MPEP § 2145 X.D.3. Based on the results of the survey conducted by Buck, one of ordinary skill would not have been motivated to select an oligonucleotide consisting of SEQ ID NO:1. In fact, one would have been led away from such an oligo.

Second, Buck's empirical study of sequencing primers would also not have led one of ordinary skill to the oligonucleotide of claim 1. None of the sequencing primers submitted or used in the study was greater than 24 nucleotides in length (see Buck, Table 1), whereas SEQ ID NO:1 is 27 nucleotides long. The Office cites the results of the empirical study as "evidence of the equivalence of primers." Office action, page 6. Applicants respectfully disagree that Buck stands for the proposition that any primer of any length and any parameters would be equivalent for sequencing methods. The Office action states (at page 6) that: "When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked." This result is hardly surprising in that Buck asked experienced sequencing laboratories to provide up to three of what they predicted to be the "best primers" from within the test sequence. See Buck, page 529, right column. All of these "best primers" fell within a fairly narrow range of lengths from 16-24 nucleotides, all shorter than the 27-nucleotide-long SEQ ID NO:1. See Buck, Table 1. Buck also found that each of the panel of 95 control primers also was effective for sequencing. However, all of the control primers tested were only 18 nucleotides long, far shorter than SEQ ID NO:1. Based on the empirical study disclosed by Buck, one of ordinary skill would have focused on oligonucleotide primers having a length in the range of 16-24 nucleotides. The Office has not suggested any reason one of ordinary skill would discard that teaching of Buck and instead select an oligonucleotide that is over 24 nucleotides in length, much less one consisting of the particular 27 nucleotides of SEQ ID NO:1.

Even if one of ordinary skill were motivated to combine the disclosures of Buck and GenBank Accession No. AF127519, and to ignore Buck's teachings regarding preferred length and G+C content as discussed above, at most the combined disclosure would be a large genus of oligonucleotides of 15-40 nucleotides in length that span the 140-nucleotide sequence. Taking

into account both DNA strands, there are 5902 possible oligonucleotides of 15-40 nucleotides in length that can be created from the sequence disclosed in GenBank Accession No. AF127519. However, the office action has provided no reason why one of ordinary skill would select the particular oligonucleotide of SEQ ID NO:1 as a PCR primer for amplifying a region of the thymidylate synthase promoter, out of all of these combinatorial possibilities. In fact, one of ordinary skill presented with the disclosure of Marsh or GenBank Accession No. AF127519 and Buck would likely not select SEQ ID NO:1, because its parameters fall outside of the range disclosed by Buck as "acceptable."

Additionally, the oligonucleotide of claim 1 has the particularly useful property of distinguishing the 2R and 3R promoter alleles based on hybridization conditions, which is not suggested by any of Marsh, GenBank Accession No. AF127519, and Buck, alone or in combination. Buck contains no disclosure related to the thymidylate synthase gene or allele identification in general. Although Marsh discloses that polymorphisms of the thymidylate synthase promoter exist, the only means for detection disclosed are PCR-length analysis and sequencing. No teaching or suggestion is made to determine promoter polymorphism status by means of hybridization analysis, which is the rationale for using the particular oligonucleotides specified in the claims.

Further, the Office action (at page 6) alleges that:

> PCR amplification is *currently* one of the fastest, cheapest way of detecting presence of any given nucleic acid, provided some information is available based on which amplification flanking the region to be amplified can be designed. Similarly quantitative FRET detection is very sensitive method capable of detecting even one molecule.

Emphasis added. The proper time frame for an obviousness analysis is not the *current* time of preparing an Office action, but rather the time when the invention was made. Further, no evidence of the usefulness or sensitivity of FRET can be found in Marsh or Buck. The above statement provides evidence that the Office's conclusion of obviousness is based on improper hindsight reasoning.

Based on at least the above arguments, applicants submit that claim 1 would not have been obvious over the combination of Marsh or GenBank Accession No. AF127519 and Buck.

Rather, the Office's conclusion of obviousness is based at least in part on improper hindsight reasoning. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 24 was rejected as allegedly being unpatentable over Luo et al., 2002, Biochem. Genet., 40:41-51 ("Luo") in view of Buck. Applicants respectfully traverse the rejection.

The Office action states (at page 7): "Regarding claim 24, Luo et al. teach sequence of a region comprising the claimed sequence of the oligonucleotide identified by SEQ ID NO 2." This is incorrect. Luo does not teach or suggest nucleic acids comprising or consisting of SEQ ID NO:2. As can be seen in the alignment presented on page 8 of the action, there is one mismatch between SEQ ID NO:2 and the sequence presented by the Office as being derived from Luo. That mismatch is at the position corresponding to nucleotide 41 of SEQ ID NO:2.

The Office cites Buck as allegedly providing motivation to create an oligonucleotide having a sequence consisting of SEQ ID NO:2 based on the disclosure of Luo. The Office action states (at pages 8-9):

> It would have been prima facie obvious to one of ordinary skill in the art at the time [] the invention was made to have used the method of Buck et al. to design the [] oligonucleotide claimed in instant application as SEQ ID No 2 using the teaching of sequences of thymidylate [synthase] enhancer region taught by Luo et al. as the starting point. One of ordinary skill in the art knows oligo containing one internal mismatch will still hybridize to the sequences of thymidylate [synthase] enhancer region.

Applicants respectfully disagree that the combination of Luo and Buck would have provided motivation to one of skill in the art to select an oligonucleotide consisting of SEQ ID NO:2. As discussed above, Buck does not teach or suggest a method of oligonucleotide design. Rather, Buck discloses (i) a survey of laboratories that designed sequencing and PCR primers to determine what they believed to be optimal and acceptable primer characteristics; and (ii) an empirical study of primers provided by those laboratories and predicted to be effective for sequencing a specific DNA sequence, as compared to a control panel of 18-nucleotide primers that spanned the sequence. See Buck pages 529, middle column, to 530, middle column, and page 532. Applicants will discuss separately the relevance of each of these disclosures to claim 24.

First, the survey of laboratories would not have led one of ordinary skill to the oligonucleotide of claim 24. The results of the survey are summarized in Table 1. The surveyed laboratories indicated that acceptable sequencing or PCR primers would range in lengths from 15 to 40 nucleotides with a G+C content of 30%-70%. Buck, Table 1. In contrast, SEQ ID NO:2 is 50 nucleotides long and has a G+C content of 78%, outside of the ranges of values for both length and G+C content deemed acceptable by the surveyed laboratories. As noted above, Buck discloses that the percent G+C was rated by the surveyed laboratories as one of the most important characteristics to consider when designing primers. Buck, page 535, left column. The results of this survey are evidence of the conventional wisdom regarding the selection of sequencing or PCR primers, and the oligonucleotide of claim 24 does not conform to this conventional wisdom. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. MPEP § 2145 X.D.3. Based on the results of the survey conducted by Buck, one of ordinary skill would not have been motivated to select an oligonucleotide having the properties of SEQ ID NO:2—in fact, one would have been led away from such an oligonucleotide.

Second, Buck's empirical study of sequencing primers would also not have led one of ordinary skill to the oligonucleotide of claim 24. None of the sequencing primers submitted or used in the study were greater than 24 nucleotides in length (see Buck, Table 1), whereas SEQ ID NO:2 is 50 nucleotides long. The Office cites the results of the empirical study as "evidence of the equivalence of primers." Office action, page 6. Applicants respectfully disagree that Buck stands for the proposition that any primer of any length and any parameters would be equivalent for sequencing methods. The Office action states (at page 6) that: "When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked." This result is hardly surprising in that Buck asked experienced sequencing laboratories to provide up to three of what they predicted to be the "best primers" from within the test sequence. See Buck, page 529, right column. All of these "best primers" fell within a fairly narrow range of lengths from 16-24 nucleotides, significantly shorter than the 50-nucleotide-long SEQ ID NO:2. See Buck, Table 1. Buck also found that each of the panel of 95 control primers also was effective for sequencing. However, all of the control primers tested were only 18 nucleotides long, less than half the length of SEQ ID NO:2. Buck does not say

suggest that a primer of 50 nucleotides would be as useful for sequencing as the much shorter primers tested. Nor does Buck provide a reason to go to the trouble to make a longer primer, when a shorter one would apparently work fine. Based on the empirical study disclosed by Buck, one of ordinary skill would not have been motivated to select an oligonucleotide having the properties of SEQ ID NO:2.

Additionally, no reasoning has been provided why one of ordinary skill would select an oligonucleotide with a one nucleotide mismatch as a primer for PCR amplification. The Office action merely states (at page 9): "One of ordinary skill in the art knows oligo containing one internal mismatch will still hybridize to the sequences of thymidylate [synthase] enhancer region." The Office does not say why one of ordinary skill would deliberately choose to introduce a mismatch, and at that particular place, so does not begin to establish that there was a motivation to do so. Neither Luo nor Buck, alone or in combination, provides any teaching or suggestion related to oligonucleotides that are not exact matches of the template sequence. In fact, of the 164 primers tested by Buck, all were apparently exactly complementary to the target DNA.

Even if one of ordinary skill were motivated to combine the disclosures of Buck and Luo, at best the combined disclosure would be a large genus of oligonucleotides of 15-40 nucleotides in length that span the 165-nucleotide sequence disclosed in Luo. For the sake of argument only, we will also discuss the genus of oligonucleotides of 15-50 in length. Taking into account both DNA strands, there are 7150 possible oligonucleotides of 15-40 nucleotides in length and 9540 possible oligonucleotides of 15-50 nucleotides in length that can be created from the sequence disclosed in Luo. Taking into account the possibility of each oligonucleotide having a one nucleotide difference as compared to the sequence disclosed in Luo, there are 311,820 possible oligonucleotides of 15-50 nucleotides in length. The office action has provided no reason why one of ordinary skill would select the particular oligonucleotide of SEQ ID NO:2 as a PCR primer for amplifying a region of the thymidylate synthase promoter from the combinatorial possibilities described. In fact, one of ordinary skill presented with the disclosure of Luo and Buck would be led away from selecting SEQ ID NO:2, both because its parameters fall outside of the range disclosed by Buck as "acceptable", and because Buck focuses solely on primers that are exact matches of the template sequence.

Further, the Office action (at page 9) alleges that:

> PCR amplification is *currently* one of the fastest, cheapest way of detecting presence of any given nucleic acid, provided some information is available based on which amplification flanking the region to be amplified can be designed. Similarly quantitative FRET detection is very sensitive method capable of detecting even one molecule.

Emphasis added. Applicants remind the Examiner that the proper time frame for an obviousness analysis is not the *current* time, i.e., when the Office action was prepared, but rather the time when the invention was made. Further, no evidence of the usefulness or sensitivity of FRET can be found in Marsh or Buck. The above-quoted statement suggests that the Office's conclusion of obviousness is based on improper hindsight reasoning.

Based on at least the above arguments, applicants submit that the oligonucleotide of claim 24 would not have been obvious over the combination of Luo and Buck. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 16 was rejected as allegedly being unpatentable over Marsh, Luo, Buck, and Stratagene 1988 catalog ("Stratagene"). Applicants respectfully traverse the rejection with respect to claim 16 and new claims 30 and 31, which depend from claim 16.

The Office action states (at page 11):

> Regarding claim 16, Marsh et al. and Buck et al. teach (a) a first oligonucleotide, the sequence of which consists of SEQ ID NO: 1 or the exact complementary sequence thereof (see details in claim 1 above).

For at least the reasons discussed above, applicants do not agree that the combination of Marsh and Buck would have made obvious an oligonucleotide consisting of SEQ ID NO:1. Additionally, the Office's rejection of claim 1 provides no findings regarding the obviousness of an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:1. Applicants submit that an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:1 would also have been nonobvious in view of Marsh and Buck.

The Office action continues (at page 11):

> Regarding claim 16, Luo et al. and Buck et al. teach (b) a second oligonucleotide, the sequence of which consists of SEQ ID NO:2 or the exact complementary sequence thereof (see details in claim 24 above).

For at least the reasons discussed above, applicants do not agree that the combination of Luo and Buck would have made obvious an oligonucleotide consisting of SEQ ID NO:2. Additionally, the rejection of claim 24 provides no findings regarding the obviousness of an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:2. Applicants submit that an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:2 would also have been nonobvious in view of Luo and Buck.

The Office action then states (at page 11):

> Regarding claim 16, none of the above references Marsh et al.; Luo et al. or Buck et al. teach a kit format.
>
> Regarding claim 16, Stratagene catalog 1988 teaches use of kit format. Stratagene 1988 teaches kits for gene characterization and they also have it for hybridizing nucleic acids.
>
> It would have been prima facie obvious to one of ordinary skill in the art to package the oligonucleotide taught by Marsh et al.; Luo et al. and Buck et al. for determination of number of polymorphic repeats present in the regulatory portion of thymidylate synthase gene in form of kit as taught by Stratagene, at the time the invention was made.

Applicants respectfully disagree. First, Stratagene provides no clear and unambiguous disclosure of kits comprising even one oligonucleotide, let alone two. Stratagene discloses that the kits contain "materials," "reagents," and "buffers," but does not specify that any of these materials or reagents comprise oligonucleotides.

Additionally, there is no motivation in any of Marsh, Luo, Buck, and Stratagene, singly or in combination, to combine the specific oligonucleotides of SEQ ID NO:1 (or its exact complement) and SEQ ID NO:2 (or its exact complement) in kits or otherwise for the "determination of polymorphic repeats present in the regulatory portion of thymidylate synthase gene" as alleged by the Office. Buck studied the use of primers for PCR and sequencing, and has no disclosure related to any other uses. Both Marsh and Luo evaluated thymidylate synthase polymorphisms by PCR and sequencing methods and contain no disclosure related to determining the number of repeats by hybridization methods. Stratagene discloses "kits that provide the materials to . . . hybridize nucleic acids." However, Stratagene provides no teaching or suggestion of the use of hybridization methods for determining a subject's genotype, much less determining the genotype of a subject with regard to the thymidylate synthase promoter.

There is simply no motivation in the references cited to combine the claimed oligos for determination of promoter polymorphisms, as alleged by the Office.

Applicants further note that the combination of oligonucleotides claimed in claims 16, 30, and 31 provides beneficial results not taught or suggested by any of Marsh, Luo, Buck, and Stratagene, either singly or in combination. The standard method of determining polymorphisms is by amplifying genomic DNA and analyzing amplicon size by gel electrophoresis, which is laborious and time-consuming. See the specification, paragraph [0009]. The present combination of oligonucleotides can be used in fast, convenient hybridization methods to identify the number of tandem repeats in the promoter region of a human thymidylate synthase gene. The number of tandem repeats can be used to predict the responsiveness of a subject towards antitumor agents such as 5-fluorouracil. The claimed oligonucleotides can therefore be used in improved methods of tumor therapy. None of these advantages could have been predicted from what was taught in the cited references.

Based on at least the above arguments, applicants submit that claim 16 would not have been obvious over the combination of Marsh, Luo, Buck, and Stratagene. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 17 and was rejected as allegedly being unpatentable over Marsh, Luo, Buck, and Stratagene, and further in view of Dobrowolski et al., US 2004/0219557 ("Dobrowolski"). Applicants respectfully traverse the rejection.

The Office action (at page 12) states:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the guidelines and principles taught by Dobrowolski et al. to design the oligonucleotide claimed in the instant application as primer/probes to be used for detection of insertion or deletion polymorphisms in the thymidylate synthase regulatory region present in human population as taught to one of ordinary skill by Marsh et al. and Luo et al.

Dobrowolski is characterized by the Office as providing the general concepts of labeling of oligonucleotides with detectable labels, e.g., FITC and RED640, and detection of polymorphisms using hybridization probes. However, the methods of Dobrowolski would not be directly applicable to analyzing TS promoter polymorphisms. All of the polymorphisms

described in Dobrowolski (i.e., single nucleotide substitutions and a deletion of seven nucleotides with a concomitant insertion of three nucleotides at the same position) are substantially different from the TS promoter polymorphisms (i.e., differences in the number of tandem repeats in the promoter region). The Dobrowolski methods rely on differential hybridization of the probes or primers to sequences that differ from each other in at least one nucleotide.[2] In contrast, the TS promoter polymorphisms do not have different or unique sequences, but rather a change in the number of identical 28-bp repeats. The oligonucleotides of the claimed kits detect differences in the number of repeats by virtue of the SEQ ID NO:1 oligonucleotide's hybridizing differentially between the perfect repeats and a downstream imperfect repeat. This can be observed in Figure 1 of the instant application. When the oligonucleotides hybridize to the **3R-type** promoter, SEQ ID NO:1 makes a perfect Watson-Crick match with the promoter sequence. In contrast, when the oligonucleotides hybridize to the **2R-type** promoter, SEQ ID NO:1 hybridizes with five out of eight nucleotides mismatched at the 3' end of the SEQ ID NO:1 oligonucleotide. Because of these mismatches in the **2R-type** promoter, SEQ ID NO:1 can hybridize to the **3R-type** promoter under more stringent conditions than it can hybridize to the **2R-type** promoter, allowing for identification of the number of tandem repeats. Such a method is neither taught nor suggested by Marsh, Luo, Stratagene, or Dobrowolski, nor any combination thereof. Therefore, the claims are unobvious over the combination, and applicants request reconsideration and withdrawal of the rejection.

Claim 19 was rejected as allegedly being unpatentable over Marsh, Luo, Buck, and Stratagene. Applicants respectfully traverse the rejection with respect to claim 19 and new claims 32 and 33, which depend from claim 19.

The Office action states (at page 14):

> Regarding claim 19, Marsh et al. and Buck et al. teach (a) a first oligonucleotide, the sequence of which consists of SEQ ID NO: 1 or the exact complementary sequence thereof (see details in claim 1 above).

[2] I.e., the polymorphisms create unique sequences that are not found in the wild-type form of the gene encoding the biotinidase enzyme.

For at least the reasons discussed above, applicants do not agree that the combination of Marsh and Buck would have made obvious an oligonucleotide consisting of SEQ ID NO:1. Additionally, the Office's rejection of claim 1 provides no findings regarding the obviousness of an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:1. Applicants submit that an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:1 would also have been nonobvious in view of Marsh and Buck.

The Office action continues (at page 14):

> Regarding claim 19, Luo et al. and Buck et al. teach (b) a second oligonucleotide, the sequence of which consists of SEQ ID NO:2 or the exact complementary sequence thereof (see details in claim 24 above).

For at least the reasons discussed above, applicants do not agree that the combination of Luo and Buck would have made obvious an oligonucleotide consisting of SEQ ID NO:2. Additionally, the rejection of claim 24 provides no findings regarding the obviousness of an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:2. Applicants submit that an oligonucleotide consisting of the exact complementary sequence of SEQ ID NO:2 would also have been nonobvious in view of Luo and Buck.

The Office action then states (at page 14):

> Regarding claim 19, none of the above references Marsh et al.; Luo et al. or Buck et al. teach a kit format.
>
> Regarding claim 19, Stratagene catalog 1988 teaches use of kit format. Stratagene 1988 teaches kits for gene characterization and they also have it for hybridizing nucleic acids.
>
> It would have been prima facie obvious to one of ordinary skill in the art to package the oligonucleotide taught by Marsh et al.; Luo et al. and Buck et al. for determination of number of polymorphic repeats present in the regulatory portion of thymidylate synthase gene in form of kit as taught by Stratagene, at the time the invention was made.

Applicants respectfully disagree. First, Stratagene provides no clear and unambiguous disclosure of kits comprising even one oligonucleotide, let alone two. Stratagene discloses that the kits contain "materials," "reagents," and "buffers," but does not specify that any of these materials or reagents comprise oligonucleotides.

Additionally, there is no motivation in any of Marsh, Luo, Buck, and Stratagene, singly or in combination, to combine the specific oligonucleotides of SEQ ID NO:1 (or its exact

complement) and SEQ ID NO:2 (or its exact complement) in kits or otherwise for the "determination of polymorphic repeats present in the regulatory portion of thymidylate synthase gene" as alleged by the Office. Buck studied the use of primers for PCR and sequencing, and has no disclosure related to any other uses. Both Marsh and Luo evaluated thymidylate synthase polymorphisms by PCR and sequencing methods and contain no disclosure related to determining the number of repeats by hybridization methods. Stratagene discloses "kits that provide the materials to . . . hybridize nucleic acids." However, Stratagene provides no teaching or suggestion of the use of hybridization methods for determining a subject's genotype, much less determining the genotype of a subject with regard to the thymidylate synthase promoter. There is simply no motivation in the references cited to combine the claimed oligos for determination of promoter polymorphisms, as alleged by the Office.

Applicants further note that the combination of oligonucleotides claimed in claims 19, 32, and 33 provides beneficial results not taught or suggested by any of Marsh, Luo, Buck, and Stratagene, either singly or in combination. The standard method of determining polymorphisms is by amplifying genomic DNA and analyzing amplicon size by gel electrophoresis, which is laborious and time-consuming. See the specification, paragraph [0009]. The present combination of oligonucleotides can be used in fast, convenient hybridization methods to identify the number of tandem repeats in the promoter region of a human thymidylate synthase gene. The number of tandem repeats can be used to predict the responsiveness of a subject towards antitumor agents such as 5-fluorouracil. The claimed oligonucleotides can therefore be used in improved methods of tumor therapy. None of these advantages could have been predicted from the disclosures of the cited references.

Based on at least the above arguments, applicants submit that claim 19 would not have been obvious over the combination of Marsh, Luo, Buck, and Stratagene. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 25 was rejected as allegedly being unpatentable over Marsh and Buck, as applied to claim 1, and further in view of Dobrowolski. Applicants respectfully traverse the rejection.

The Office action states (at page 16): "Regarding claim 25, Marsh et al. and Buck et al. teach the oligonucleotide of claim 1 but do [not] teach wherein the oligonucleotide is labeled

with a detectable label." For at least the reasons discussed above, applicants do not agree that the oligonucleotide of claim 1 would have been obvious over the combination of Marsh and Buck. Dobrowolski does not remedy the deficiencies of Marsh and Buck. Dobrowolski provides no teaching related to the thymidylate synthase promoter or any sequence comprising SEQ ID NO:1. Further, Dobrowolski is silent regarding methods of selecting oligonucleotides for hybridization analysis. Therefore, applicants submit that claim 25 is patentable over the combination of Marsh, Buck, and Dobrowolski.

Claim 26 was rejected as allegedly being unpatentable over Luo and Buck, as applied to claim 24, and further in view of Dobrowolski. Applicants respectfully traverse the rejection.

The Office action states (at page 17): "Regarding claim 26, Luo et al. and Buck et al. teach the oligonucleotide of claim 24 but do [not] teach wherein the oligonucleotide is labeled with a detectable label." For at least the reasons discussed above, applicants do not agree that the oligonucleotide of claim 24 would have been obvious over the combination of Luo and Buck. Dobrowolski does not remedy the deficiencies of Luo and Buck. Dobrowolski provides no teaching related to the thymidylate synthase promoter or any sequence comprising SEQ ID NO:2. Further, Dobrowolski is silent regarding methods of selecting oligonucleotides for hybridization analysis. Therefore, applicants submit that claim 26 is patentable over the combination of Luo, Buck, and Dobrowolski.

Claim 27 was rejected as allegedly being unpatentable over Marsh, Luo, Buck, Stratagene, and Dobrowolski, as applied to claim 17 above, and further in view of Pals et al., 2001, J. Biochem. Biophys. Methods, 47:121-129 ("Pals"). Applicants respectfully traverse the rejection. As discussed above, applicants disagree that the kit of claim 17 would have been obvious over the combination of Marsh, Luo, Buck, Stratagene, and Dobrowolski. Pals does not remedy the deficiencies of this combination of references. Pals is cited by the Office as allegedly disclosing that "the upstream end (5' end) of the first oligonucleotide is labeled with the fluorescent dye RED 705." Office action, page 19. Pals provides no disclosure related to the thymidylate synthase promoter, and no teaching or suggestion of the use of the claimed oligonucleotides in methods of identifying the number of tandem repeats in the promoter region

of a human thymidylate synthase gene. Applicants therefore submit that claim 27 is nonobvious in view of Marsh, Luo, Buck, Stratagene, Dobrowolski, and Pals, and applicants request reconsideration and withdrawal of the rejection.

Claim 28 was rejected as allegedly being unpatentable over Marsh and Buck in view of Stratagene. Applicants respectfully traverse the rejection. The Office action states (at page 20):

> Regarding claim 28, Marsh et al. in view of Buck et al. teach
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> (i) the oligonucleotide of claim 1 (see details above in claim 1) and
>
> (ii) a second oligonucleotide that hybridizes to the region adjacent to the 5' side of the oligonucleotide of claim 1. (Marsh et al. teach the tandem repeat sequence in a thymidylate synthase promoter enhancer region (see page 310 abstract). The oligo of claim 1 is part of this region taught by Marsh et al. The upstream sequence on the 5' side of the oligonucleotide of claim 1 in the thymidylate synthase promoter enhancer region is taught by Marsh et al.
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to design a second oligonucleotide using the method of Buck et al. such that this second oligonucleotide hybridizes to the region adjacent to the 5' side of the oligonucleotide of claim 1 using the thymidylate synthase promoter enhancer region taught by Marsh et al. as starting point.

For at least the reasons discussed above, applicants do not agree that the combination of Marsh and Buck would have made obvious an oligonucleotide consisting of SEQ ID NO:1. Additionally, there is no motivation in any of Marsh, Buck, and Stratagene, singly or in combination, to combine the oligonucleotide of SEQ ID NO:1 with a second oligonucleotide that hybridizes to the region adjacent to the 5' side of the oligonucleotide in kits or otherwise for the "determination of polymorphic repeats present in the regulatory portion of thymidylate synthase gene" as alleged by the Office. Office action, page 22. Buck studied the use of primers for PCR and sequencing, and has no disclosure related to any other uses. Marsh evaluated thymidylate synthase polymorphisms by PCR and sequencing methods and contains no disclosure related to determining the number of repeats by hybridization methods. Stratagene discloses "kits that provide the materials to . . . hybridize nucleic acids." However, Stratagene provides no teaching or suggestion of the use of hybridization methods for determining a subject's genotype, much less determining the genotype of a subject with regard to the thymidylate synthase promoter.

There is simply no motivation in the references cited to combine the claimed oligos for determination of promoter polymorphisms, as alleged by the Office.

Additionally, the combination of oligonucleotides claimed in claim 28 provides beneficial results not taught or suggested by any of Marsh, Buck, and Stratagene, either singly or in combination. The standard method of determining polymorphisms is by amplifying genomic DNA and analyzing amplicon size by gel electrophoresis, which is laborious and time-consuming. See the specification, paragraph [0009]. The present combination of oligonucleotides can be used in fast, convenient hybridization methods to identify the number of tandem repeats in the promoter region of a human thymidylate synthase gene. The number of tandem repeats can be used to predict the responsiveness of a subject towards antitumor agents such as 5-fluorouracil. The claimed oligonucleotides can therefore be used in improved methods of tumor therapy.

Based on at least the above arguments, applicants submit that claim 28 would not have been obvious over the combination of Marsh, Buck, and Stratagene. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 29 was rejected as allegedly being unpatentable over Marsh, Buck, and Stratagene, as applied to claim 28 above, and further in view of Pals. Applicants respectfully traverse the rejection. Applicants respectfully traverse the rejection. As discussed above, applicants disagree that the kit of claim 28 would have been obvious over the combination of Marsh, Buck, and Stratagene. Pals does not remedy the deficiencies of this combination of references. Pals is cited by the Office (at page 23) as allegedly disclosing that:

> the 5' end of the oligonucleotide of (i) is labeled with the fluorescent dye RED 640 or RED705 (See page 121 abstract where the 3' probes, are taught to labeled at 5' end with LCREd 640 (wild type probe) or LCRED 705 (mutant probe)), and
>
> the 3' end of the oligonucleotide of (ii) is labeled with the fluorescent dye FITC (See page 121 abstract where the 5'-probe is taught to be 3' labeled with FITC).

Pals provides no disclosure related to the thymidylate synthase promoter, and no teaching or suggestion of the use of the claimed oligonucleotides in methods of identifying the number of

tandem repeats in the promoter region of a human thymidylate synthase gene. Applicants submit that Pals does not remedy the deficiencies of Marsh, Buck, and Stratagene, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Upon a finding that claim 1 is allowable, applicants request rejoinder of withdrawn method claims 6-15, all of which depend directly or indirectly from claim 1.

This reply is being submitted with a Request for Continued Examination, a Petition for Extension of Time, and the required fees. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 18201-0003US1.

Respectfully submitted,

Date: December 23, 2009

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